CHAPTER 5

ACE inhibitors and the risk of urinary tract infections: Comparison of a case-crossover and prescription sequence symmetry design

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This chapter is based on the published manuscript:
Abstract

Background
In a post-hoc analysis of a randomized controlled trial (RCT) and a prescription sequence symmetry analysis (PSSA) we observed that angiotensin-converting enzyme inhibitor (ACEi) use was associated with an increased risk of urinary tract infections (UTIs). We evaluated the same association using a case-crossover design.

Methods
A case-crossover design was performed with the University Groningen prescription database (IADB.nl). The first date of incident use of nitrofurantoin, used as a proxy for UTIs, was defined as the index date. The risk period was defined as 30 days before the index date and the control period as 60-90 days before that date. A person was considered exposed to ACEi if there was at least three days’ supply within the time-window. In secondary analysis the definitions were set similar to the previous PSSA. Conditional logistic regression with adjustments for potential time-varying confounders was applied to obtain adjusted odds ratios.

Results
There were 51,249 patients that received a first nitrofurantoin prescription and met eligibility criteria. Of these, 276 patients were only exposed to ACEi during the risk window and 150 patients only during the control window (crude OR 1.84, 95%CI 1.51-2.25; adjusted OR 1.74, 95%CI 1.42-2.13). When using similar criteria as in the PSSA, the case-crossover estimates were slightly higher (adjusted OR 2.09, 95%CI 1.68-2.61).

Conclusions
These findings suggest that ACEi use increases the risk of developing first UTIs. Despite the similarities between the case-crossover design and the PSSA, the PSSA led to slightly lower effect estimates than the case-crossover design and the RCT.
Introduction

Randomized clinical trials (RCTs) are considered to provide evidence of the highest grade on treatment effects whereas observational studies are viewed less valid because they are prone to confounding [1]. However, often it is not feasible or unethical to perform a RCT and observational studies on treatment effects are required to guide health care policy. To prevent or limit confounding in observational research several design methods have been developed. One group of methods that can overcome the challenging task of identifying a control group with similar patient characteristics are case-only studies. Examples include the self-controlled case-series [2], case-crossover studies [3] and sequence symmetry analyses [4, 5]. The advantage of these methods is that patients can serve as their own controls, thereby eliminating confounding by (unmeasured) factors that are stable over time.

Recently, we applied a prescription sequence symmetry analysis to estimate the association between angiotensin-converting enzyme inhibitors (ACEi) use and urinary tract infections (UTIs) (sequence ratio = 1.56, 95% confidence interval (CI) 1.11-2.20)) [6]. That study was conducted to further support findings from a post-hoc analysis of a randomized clinical trial in which fosinopril, an ACEi, was associated with an increased risk of incident UTIs (hazard ratio = 1.82, 95% CI 1.16-2.88) [7]. We hypothesized that the underlying mechanism may be related to an ACEi-induced reduction of the urine output [6, 8, 9]. As bacterial clearance from the urinary tract is dependent on the urine output [10], ACEi initiation may result in an increased risk of first UTIs.

In the prescription sequence symmetry analysis we could not adjust for time-varying confounders and the design has been criticized because of a lower sensitivity to detect adverse drug events than conventional observational designs [11]. Since the prescription sequence symmetry analysis can be regarded as a variation on the case-crossover design [12], it would be informative to compare the results of these two designs evaluating the same association in the same database. However, such a comparison is currently lacking from the existing literature, although a few comparisons with other designs than the case-crossover have been made [11, 13, 14]. We aimed to re-evaluate the association between ACEi initiation and UTIs using the case-crossover design, while adjusting for several potential time-varying confounders. As a secondary objective we used this empirical comparison to discuss some important differences between the sequence symmetry design and the case-crossover design.
Methods

Data source, setting and study population
The design of the earlier reported prescription sequence symmetry analysis has been published elsewhere [6]. Briefly, the analyses were performed using data retrieved from the University Groningen IADB.nl database (IADB), a community-based pharmacy prescription database containing detailed prescription data from 1994 through 2011 from approximately 55 community pharmacy, covering an estimated population of 500,000 patients [15]. All patients that were incident users of both ACEi and nitrofurantoin (a proxy for UTIs) between January 2006 and December 2011 were selected in that study. First starters or incident users were defined as patients who did not have a prescription for the study drug over a time period of 12 months or more and presence in the database for at least 12 months prior to the first prescription. The prescription sequence symmetry analysis was performed to determine whether nitrofurantoin was more often initiated after than before ACEi initiation. To reduce the probability of time-varying confounding a relatively short time-span of 4 weeks was used. The sequence ratio was calculated by dividing the number of individuals starting ACEi first and nitrofurantoin second by the number of individuals starting both drugs in the reverse order.

For the present study we used the same database to conduct a case-crossover analysis. In the primary analysis, a case-crossover design was performed using data retrieved from the IADB covering the whole data-capturing period from 1994 to 2011.

A secondary analysis was performed, thereby keeping the definitions and in- and exclusion criteria as similar as possible to the original study [6]. As the guidelines for treating UTIs have changed over the years in the Netherlands, different criteria were used to exclude persons with previous UTIs in both sets (see below).

Case-crossover design
The case-crossover design was first introduced in 1991 by Maclure [3]. With this design patients (cases) serve as their own control, thereby limiting selection bias and confounding by time-invariant characteristics. A within-person comparison is made by comparing the probability of exposure in the period just before the outcome event (risk period) with the probability of exposure in control period(s). The crude odds ratio can be calculated by dividing the number of individuals being exposed only in the risk period by the number of individuals being exposed only in the control period. However, when time-varying confounders are present, conditional logistic regression can be used to adjust for these confounders. We matched 1 control period per case, thereby avoiding
bias due to non-exchangeability of the distribution of exposures between multiple control intervals [16].

**Primary Analysis**

The date of incident use of nitrofurantoin was defined as the index date. Incident use was defined as absence of a prescription of nitrofurantoin in the 12 months prior to the dispensing date. We excluded persons using other antibiotics indicated for use against UTIs prior to their first nitrofurantoin prescription (amoxicillin, amoxicillin/clavulanate, quinolones, fosfomycin, methenamine, sulfonamides or trimethoprim). We defined the risk period as 30 days before the index date and the control period as 60-90 days before the index day. A binary exposure indicator was created for the risk and control period, such that a person was considered exposed to ACEi if there was at least 3 days’ supply within the window, thereby assuming that the exposure started on the day of dispensing. Seven days were added to the days’ supply dispensed for every dispensation to allow for modest non-adherence. In addition, binary exposures were created using the same criteria for prescription drugs that could act as potential time-varying confounders. Potential time-varying confounders were selected on prior knowledge and included the following prescription drugs: β-adrenoceptor antagonists (β-blockers), calcium channel blockers, angiotensin-receptor blockers, diuretics, lipid modifying agents, non-steroidal anti-inflammatory drugs and glucose lowering drugs. Statistical analyses were performed using SPSS version 20 (SPSS Inc, Chicago, IL).

**Secondary Analyses**

To be able to make a fair comparison with the published prescription sequence symmetry analysis [6], a secondary analysis was performed, thereby keeping the definitions and inclusion/exclusion criteria as similar as possible to the original study. The same study period was used (January 2006 – December 2011) and the risk period was defined as the 28 days before the index date and the control period as 56-84 days before the index date. In addition, individuals were considered exposed to ACEi if they had at least 1 days’ supply within the window, as done with the prescription sequence symmetry analysis [6]. Patients receiving the second- or third-choice (during the period of 2006-2011) UTI antibiotic treatment (trimethoprim and fosfomycin) in the year before their first nitrofurantoin prescription were excluded from the analysis. In sensitivity analysis we defined the risk period as 28 days before the index date and the control period as 29-56 days before the index date.
Results

There were 116,974 patients that received a nitrofurantoin prescription between January 1994 and December 2011. After excluding all patients who were not present in the database 12 months prior to their nitrofurantoin prescription or who previously received antibiotics used to treat UTIs, a total of 51,249 cases remained. Of these, 3966 patients were exposed to ACEi in the year before their first nitrofurantoin prescription. The characteristics of these patients during both comparison time windows are shown in Table 5.1. Demographic characteristics were evaluated at the index date.

The case-crossover estimates of the association between ACEi use and UTI medication are shown in Table 5.2. The crude odds ratio was 1.84 (95% CI 1.51-2.25), which slightly decreased after adjustment for time-varying prescribing of diuretics (OR 1.74, 95% CI 1.42-2.13) or for all factors listed in Table 5.1 (OR 1.74 95% CI 1.41-2.15). Although the estimates were calculated using conditional logistic regression, the crude odds ratio could also be obtained by dividing the number of patients that are exposed in the risk window and unexposed in the control window by the number of patients that are unexposed in the risk window and exposed in the control window (276 / 150 = 1.84). When the analysis were restricted to individuals within the same age-category as the previous post-hoc analysis of the randomized controlled trial (28 to 75 years of age), the adjusted odds ratio increased to 1.90 (95% CI 1.44-2.50).

Secondary analysis
When the same study period and similar criteria were used as done with the previous prescription sequence symmetry analysis [6], an adjusted odds ratio of 2.09 (95% CI 1.68-2.61) was obtained. Using a control window immediately before the risk window did not substantially affect this estimate (aOR 2.10, 95% CI 1.59-2.77).

Restricting this analysis to individuals aged 28-75 years of age, resulted in an adjusted odds ratio of 2.29 (95% CI 1.70-3.06).
Table 5.1. Characteristics of patients exposed to ACEi in the year prior their first nitrofurantoin prescription (N=3966).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Risk window</th>
<th>Control window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years); (IQR)</td>
<td>72 (62-80)</td>
<td></td>
</tr>
<tr>
<td>Women; N (%)</td>
<td>3197 (81)</td>
<td></td>
</tr>
</tbody>
</table>

### Exposure to

<table>
<thead>
<tr>
<th>Medication</th>
<th>Risk window N (%)</th>
<th>Control window N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi</td>
<td>3492 (88)</td>
<td>3366 (85)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>1622 (41)</td>
<td>1593 (40)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>786 (20)</td>
<td>774 (20)</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>206 (5)</td>
<td>192 (5)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1755 (44)</td>
<td>1692 (43)</td>
</tr>
<tr>
<td>Glucose-lowering medication</td>
<td>979 (25)</td>
<td>943 (24)</td>
</tr>
<tr>
<td>Lipid modifying medication</td>
<td>1381 (35)</td>
<td>1366 (34)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>429 (11)</td>
<td>392 (10)</td>
</tr>
</tbody>
</table>

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs

Table 5.2. Case-crossover estimates for the association between ACEi and UTIs

<table>
<thead>
<tr>
<th></th>
<th>Risk window</th>
<th>Unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control window</td>
<td>Exposed</td>
<td>3216</td>
</tr>
<tr>
<td></td>
<td>Unexposed</td>
<td>276</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Crude OR (95% CI)</td>
<td>1.84 (1.51 – 2.25)</td>
<td></td>
</tr>
<tr>
<td>Adjusted OR (95% CI)a</td>
<td>1.74 (1.42 – 2.13)</td>
<td></td>
</tr>
<tr>
<td>Adjusted OR (95%CI)b</td>
<td>1.74 (1.41 – 2.15)</td>
<td></td>
</tr>
</tbody>
</table>

*aadjusted for time-varying use of diuretics

*badjusted for time-varying use of diuretics, β-blockers, calcium channel blockers, angiotensin receptor blockers, glucose-lowering medication, lipid modifying medication and non-steroidal anti-inflammatory drugs.
Discussion

This population-based case-crossover study showed that recent use of ACEi was associated with an increased risk of starting UTI antibiotic therapy. The results confirm findings from a previous post-hoc analysis of a randomized controlled trial (HR, 1.82; 95% CI, 1.16–2.88) [7] and a prescription sequence symmetry analysis [6].

Secondary analyses showed that, using the same database and in- and exclusion criteria as similar as possible, a case-crossover design resulted in higher risk estimates than a prescription sequence symmetry design (OR 2.09, 95% CI 1.68-2.61 vs. SR 1.56, 95% CI 1.11-2.20). There are several explanations for this observation. The first one is the use of different risk estimates. However, it can be shown that the sequence ratio equals a rate ratio if there is no loss to follow-up and the same time at risk is used [4, 17], which is similar to an odds ratio obtained using a case-crossover analysis with the same short risk-intervals [18].

Another possibility is that the case-crossover analysis adjusted for several potential time-varying confounders, while no adjustment was possible using the prescription sequence symmetry analysis. However, the unadjusted case-crossover estimate was also higher than the effect estimate obtained with the prescription sequence symmetry analysis.

Another explanation may be that the prescription sequence symmetry analysis provides conservative estimates compared to other methods, as found in an empirical comparison with a cohort and nested case-control design [11]. A theoretical comparison with the self-controlled case-series could partly explain why sequence symmetry designs could provide more conservative estimates than other designs. We did not add an empirical comparison with a self-controlled case-series design as urinary tract infections within individuals are not independent of each other, which makes self-controlled case series invalid (although recently a modification was proposed to overcome this problem) [19]. Suppose one would assess the effect of drug A initiation on the occurrence of event B, thereby assuming that the occurrence of event B does not modify the risk of a subsequent event B. A self-controlled case-series would use information about the incidence of event B before and after starting with drug A within patients. Thus, if a patient experiences both an event before and after starting with drug A, both events are used in the analysis. In contrast, the variant of the sequence symmetry analysis we previously applied only takes into account the event before starting with drug A and disregards the event after starting with drug A, thereby leading to a lower effect estimate compared to a self-controlled case-series analysis.
A prescription sequence symmetry analysis can also be performed in a way that takes into account information about events before and after drug initiation within patients [20]. Instead of selecting first time users of both drugs or first time users and first events, the occurrence of both new and recurrent events before and after initiation with the drug of interest is then used to calculate a rate ratio. This rate ratio can be calculated by dividing the number of patients experiencing events only after therapy initiation by the number of patients experiencing events only before therapy initiation. However, as with the self-controlled case-series, this way of analysing the data would in our case result in an overestimation of the risk, as patients that experience an UTI before ACEi initiation would have subsequently a higher risk to experience another UTI after ACEi initiation, while a first UTI after ACEi initiation does not modify the probability of experiencing an UTI before ACEi initiation. To avoid such overestimation, and because recurrent UTIs may be more likely complicated UTIs which are more likely to be treated with other antibiotics than nitrofurantoin, we decided in our previous study [6] to analyse the data in a similar way as Hallas proposed [21].

Alternatively, despite using the same database and similar in- and –exclusion criteria, the difference may be explained by the fact that both methods partly use different patients and patient-time in the analysis. The sequence ratio is partly based on patients with a first UTI prior to ACEi initiation, while the case-crossover design selects only patients using ACEi prior to their first UTI. In our case-crossover analysis we separated the risk and control window by 30 days to overcome potential carry-over effects, although sensitivity analysis suggested that carry-over effects did not play an important role. In our previous prescription sequence symmetry analysis carry-over effects did not play a role since the sequence ratio was purely based on the order of first-time prescriptions.

An important strength of this case-crossover study is that we controlled for time-invariant confounders and largely controlled for confounders that do change minimally or slowly over time, regardless of whether these confounders were measured or not. In addition, we controlled for a large set of measured potential time-varying confounders, thereby reducing the probability that the results are affected by time-varying confounding. Further, the data were obtained from a widely researched pharmacy dispensing database which is representative for the general Dutch population in terms of drug use [15].

By using the same database and similar in- and exclusion criteria we could make an empirical comparison between the case-crossover design and a previously published prescription sequence symmetry analysis [6]. Although a few comparisons between the sequence symmetry design and other more conventional designs do exist [11,13, 14], this is the first study making the intuitive comparison with a case-crossover study.
Another strength of this study is that we evaluated a relatively unknown adverse effect. If we would have made a comparison between the case-crossover design and a prescription sequence symmetry analysis while evaluating a well-known effect, different conclusions could have been reached. A prescription sequence symmetry analysis could overestimate the effect with well-known effects, as physicians may try to avoid prescribing a drug that further increases the risk of a recently experienced event. Therefore, sequence symmetry designs seem to be most useful to detect new adverse events [6, 11, 21] although it has also been used for the evaluation of well-known adverse events [13, 22-25].

This study also has some important limitations. The case-crossover design was originally intended to study brief exposures that have an immediate effect (e.g. the association between heavy physical exertion and acute myocardial infarction) [26]. Although ACEi are in general used more chronically, the fact that the increased risk is mainly expected shortly after treatment initiation and the presence of non-adherence make the application of a case-crossover design using an exposure window of 28-30 days possible. In case all patients exposed to ACEi were receiving a life-long therapy and were perfectly adherent, a case-crossover analysis would not be possible in contrast to a prescription sequence symmetry analysis.

When comparing the results of both non-experimental designs with the post-hoc analysis of the randomized controlled trial, one should take into account that the findings from the randomized controlled trial were obtained during an average follow-up of 2.7 years (HR, 1.82; 95% CI, 1.16–2.88) of patients with microalbuminuria [7]. When the follow-up of the post-hoc analysis was restricted to 1 year, the hazard ratio was slightly higher with HR 2.43 (95% CI 1.11-5.33), although confidence intervals widely overlap (KB Pouwels, unpublished data, 2013). The size of the effect may therefore not be directly comparable with the RCT findings, although the direction of the effect is the same with all designs. For a more thorough investigation of the performance in terms of bias and precision of the case-crossover design and the prescription sequence symmetry analysis simulation studies should be performed.

Furthermore, we used nitrofurantoin prescriptions as a proxy for urinary tract infections. Although nitrofurantoin is almost exclusively used to treat urinary tract infections, this proxy has a somewhat lower sensitivity [6]. Since this misclassification is likely random, this would result in an underestimation of the effect for both designs.

We did not have information about drug use during hospitalizations and over the counter drugs. The majority of urinary tract infections will be treated outside the hospital and both antibiotics and ACEi are not available over the counter in the
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Netherlands. However, our results may be affected by immeasurable time bias during hospitalizations. Despite these limitations, we did find results that were similar to that found in a randomized setting [7].

In addition, the case-crossover and prescription sequence symmetry design produce different effect estimates (odds ratio vs sequence ratio) that may only be comparable under certain conditions. A sequence ratio and a risk ratio should approximate each other when the length of follow-up is the same in the cohort as in the prescription sequence symmetry analysis [27]. On its turn an odds ratio approximates a risk ratio if the outcome is rare. Since less than 1% of patients initiating ACEi treatment received a nitrofurantoin prescription within a time-window of 4 weeks, it seems reasonable to consider the outcome as rare in the prescription sequence symmetry analysis. Similarly, first nitrofurantoin prescriptions are expected to be rare within 4 weeks of (re-)initiating or stopping ACEi therapy, a situation in which non-collapsibility of the odds ratio is of less concern.

Finally, our results may not be generalizable to all urinary tract infections. We only considered first urinary tract infections in our analyses. Although ACEi initiation is associated with an increased risk of first UTIs, ACEi treatment may even reduce the risk of recurrent UTIs. As ACEi can inhibit rac1 membrane expression [28, 29], they may reduce bacterial invasion [30-33] and subsequently prevent the establishment of a reservoir of recurrent UTIs [34]. If this effect is stronger than the ACEi-associated reduction in urine output [8, 9], ACEi may decrease the risk of recurrent urinary tract infections, despite increasing the risk of first UTIs. However, awareness of the association between ACEi therapy initiation and the risk of first UTIs may improve adherence, especially if future research does show that ACEi can reduce the risk of recurrent UTIs.

In conclusion, these findings further support the hypothesis that ACEi therapy initiation is associated with an increased risk of developing first UTIs, even after adjustment for all potential time-invariant and several time-varying confounders. Furthermore, despite the similarities between the case-crossover design and the prescription sequence symmetry design and the use of the same database, the prescription sequence symmetry design led to slightly lower effect estimates than the case-crossover design and the analysis in a randomized setting.
Chapter 5

References


